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Statistical Analysis Plan

Date of Plan:	**2019-Jun-03**
Title:	**LIBERATE International: Evaluation of the Safety and Efficacy of the Viveve Treatment for Stress Urinary Incontinence**
Protocol Number:	**VI-17-01**
Version	**1.0**
Product:	**Viveve Treatment, SUI Protocol**
Phase:	**N/A**
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Statistical Analysis Plan Approval:

This version of the Statistical Analysis Plan has been read and approved by:

	12Jun2019
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Revision History:

Revision	Date	Description of Changes	Requested by
0.1	2018-Aug-30	Initial Document (Not signed)	Sara Nichols
1.0	2019-Jun-03	Updates requested by Viveve	Viveve

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1. TABLE OF ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
AMC	Adjusted Mean Change
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CFB	Change from Baseline
CI	Confidence Interval
CRO	Contract Research Organization
FAS	Full Analysis Set (also referred to as Intent-to-Treat)
FSFI	Female Sexual Function Index
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form
I-QOL	Incontinence Quality of Life
ITT	Intent-to-Treat (also referred to as Full Analysis Set)
LLT	MedDRA Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat Population
n	Number
PT	MedDRA Preferred Term
RF	Radiofrequency
SAE	Serious Adverse Event
SE	Standard Error
SOC	MedDRA System Organ Class
SP	Safety Population
SUI	Stress Urinary Incontinence
TEAE	Treatment-Emergent Adverse Event
UDI-6	Urogenital Distress Inventory

2. INTRODUCTION

Stress urinary incontinence (SUI) is a major challenge for many women particularly those who have experienced child birth or are menopausal. Upwards of 55% of women with a previous vaginal delivery may exhibit signs and symptoms of SUI (Tahtinen 2016). The overarching effects of SUI impact a women's health and quality of life and have been shown to result in depression, social stigma and lack of self-confidence. The need to use an external pad to absorb urine leakage from even normal daily activities such as laughing, or coughing is unsatisfactory and can be extremely inconvenient, and often embarrassing for women.

Currently available treatment options for women are limited. Pelvic floor exercises (such as Kegels) offer some benefit to a percentage of women but compliance and sustained benefit can be issues. More aggressive approaches to manage SUI include pelvic surgery, slings and mesh. These invasive options involve more risk and recovery time and are a last resort for many patients.

The gap between conservative and invasive treatment options for SUI represents an opportunity to address an enormous unmet healthcare need for women. Minimally invasive treatments for SUI would be a highly appealing solution provided they offered a safe, consistent improvement in symptoms without significant time commitment or recovery. Any effective treatment would represent a major advance in women's health.

The Viveve Procedure, SUI protocol, offers a non-surgical alternative to traditional surgery using non-ablative, monopolar radiofrequency (RF) energy to improve SUI. It induces a mild, controlled reaction in the submucosal tissues that stimulates the body to restore collagen, thereby remodeling the tissue without causing scarring.

This Statistical Analysis Plan describes the analyses planned for protocol VI-17-01 version dated 23October2018, to demonstrate that the active treatment (i.e., Viveve Treatment, SUI protocol) is superior to the sham treatment.

3. OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of the Viveve treatment, SUI protocol, in improving SUI, assessed using the change from Baseline (CFB) to 6 months post-treatment in the 1-hr Pad Weight Test.

3.2. Secondary Objectives

The secondary objective of this study includes the determination of:

- Safety of the Viveve treatment from the treatment procedure through 6 months post-treatment.

3.3. Exploratory Objectives

The exploratory objectives include the determination of:

- Efficacy in decreasing the 1-hr pad weight at 3 months post-treatment.
- Efficacy in decreasing the 24-hr pad weight at 6 months post-treatment.
- Efficacy in reducing the number of incontinence episodes in the 3-day bladder voiding diary at 3 and 6 months post-treatment.
- Quality of Life benefits as measured by changes from Baseline to 3 and 6 months post-treatment in the Urogenital Distress Inventory (UDI-6), International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form (ICIQ-UI-SF) and Incontinence Quality of Life (I-QOL).
- Efficacy to improve Female Sexual Function Index (FSFI) total score from Baseline to 3 and 6 months post-treatment, in subjects with FSFI total score ≤26.5 at Baseline.

4. VARIABLES

4.1. Response Variables

4.1.1. Primary Endpoints

The primary efficacy endpoint for this trial is:

- CFB to 6 months post-treatment in the 1-hr Pad Weight Test.

4.1.2. Secondary Endpoints

4.1.3. Safety Endpoints

Safety endpoints for this trial include:

- Safety as assessed by adverse event (AE) reporting from the treatment procedure to study completion for each subject.

4.1.4. Exploratory Endpoints

Exploratory endpoints for this trial include:

- CFB to 3 months post-treatment in 1-hr pad weight
- CFB to 6 months post-treatment in 24-hr pad weight
- CFB to 3 and 6 months post-treatment in 3-day bladder voiding diary
- CFB to 3 and 6 months post-treatment in UDI-6, ICIQ-UI-SF and I-QOL.
- CFB to 3 and 6 months post- treatment in FSFI total score, in subjects with FSFI total score ≤26.5 at screening

5. STATISTICAL ANALYSIS ISSUES

5.1. Populations to be Analyzed

Subjects in the following population will be enrolled and analyzed in this study: pre-menopausal (≥18 age) female subjects with a normal, or abnormal but not clinically significant, physical, pelvic and neurologic exam; 1-hr pad weight at Baseline ranging from ≥5 to ≤50 g as the net increase from the pre-test pad weight; and a minimum of 1 incontinence episode per day as determined in the 3-day voiding diary.

5.1.1. Analysis Populations

The analysis populations will consist of subjects categorized into the 3 populations described below.

5.1.1.1 Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects and is also known as the intention-to-treat (ITT) population. The FAS will be used for all efficacy analyses.

5.1.1.2 Modified Intent-to-Treat Population

The Modified ITT (mITT) includes all randomized subjects who are treated and complete the study. The mITT will be used for confirmatory analysis of efficacy endpoints.

5.1.1.3 Safety Population

The Safety Population (SP) includes all randomized subjects in whom the treatment procedure is started, regardless of if the procedure is completed. The SP will be used for all of the safety summaries.

5.2. Statistical Analysis of Primary Measures

The primary efficacy endpoint for this study is CFB to 6 months post-treatment in 1-hr pad weight. Analysis of covariance (ANCOVA) with treatment group, study site and Baseline 1-hr pad weight as independent variables, will be used to analyze the primary efficacy endpoint. The FAS will be used, with subjects included in their randomized treatment group regardless of the treatment they actually received. The Baseline 1-hr pad weight is defined as the 1-hr pad weight at the Screening Visit. Missing values for the 6 month 1-hr pad weight will be imputed using a multiple imputation method that assumes the data are missing at random. Imputed datasets will be analyzed using an ANCOVA model with treatment group, study site, and Baseline 1-hr pad weight as independent variables. Approximately 100 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. The adjusted mean change (AMC) and standard error (SE) will be provided for both treatment groups, along with the difference in AMC, its 95% confidence interval (CI) and associated p-value. The AMCs for each study site will also be provided.

Assuming the data is missing at random and the pattern of missing data is monotone the following generalized code will be used.

```
PROC MI data=Widedataset noprint out=outmi seed=501213  NIMPUTE = 100;
class Treatment Site; /* */
monotone reg (CFB /details);
var Treatment Site V1PW CFB ;
run;

/* NOTE: Although currently shown below together in one model PROC MIXED may
need to be run twice once for the lsmeans and once for the differences, in order to
work well in MIANALYZE.*/

PROC MIXED data=outmi;
class Treat Site;
model CFB = Treatment V1PW Site /solution covb;
lsmeans treat/ pdiff cl;
by _imputation_;
ods output solutionf=mxparms CovB=mxcovb lsmeans=lsmeans_ds(drop=effect)
diffs=pdiff  ;
run;

PROC MIANALYZE
SAS Usage Note 30715 (link provided in references) will be modified appropriately
and used to transfer the data between PROC MIXED and PROC MIANALYZE for the
lsmeans and their differences
```

Note1: To facilitate transfer of data between PROCs, the Treatment variable will contain only 1 word treatment descriptions: Viveve or Sham, likewise for Site, e.g. 201, 202

A confirmatory analysis of the primary efficacy endpoint will be performed using the FAS and same ANCOVA as the primary analysis, but using only observed case data (no imputation will be performed for missing data). A second confirmatory analysis of the primary efficacy endpoint will be performed using the mITT, using only observed case data.

5.3. Exploratory Efficacy Endpoint Analyses

Exploratory efficacy endpoints include CFB to 3 months post-treatment in 1-hr pad weight; CFB to 6 months post-treatment in 24-hr pad weight; CFB to 3 and 6 months post-treatment in 3-day bladder voiding diary; CFB to 3 and 6 months post-treatment in UDI-6, ICIQ-UI-SF and I-QOL; and CFB to 3 and 6 months post-treatment in FSFI total score, in subjects with FSFI total score ≤26.5 at Baseline. For the exploratory efficacy endpoints a significance level of 0.05 will be used; given the large number of endpoints, the p values for those endpoints will be considered descriptive.

Scoring of the UDI-6, ICIQ-UI-SF, I-QOL, and FSFI questionnaires is described in the separate Questionnaire Completion and Scoring Guideline document. Included in that document are rules for obtaining the total score for each questionnaire. The impact of missing items on the total score is discussed. If the total score cannot be computed based on the rules provided, e.g. there are too many items with no response, no further

imputation will be implemented. This lack of imputation matches the handling of other exploratory endpoints discussed in the paragraph below.

Each of the continuous endpoints will be analyzed using ANCOVA with treatment group, study site, and the relevant Baseline as independent factors. The FAS population will be used for each analysis (for the FSFI analyses, the FAS subjects with a Baseline FSFI total score ≤26.5 will be used), with subjects included in their randomized treatment group regardless of the treatment they actually received. Baseline for each endpoint is the relevant value from the Screening Visit. For each of the exploratory endpoints, only observed case data will be used (no imputation will be performed for missing data). Output from each ANCOVA will include the AMC and SE for the active treatment and sham groups, as well as the difference in AMC, its 95% CI, and p-value. The AMCs for each study site will also be provided for each ANCOVA.

Confirmatory analyses will be performed for each of the exploratory endpoints, using the mITT with observed case data only (no imputation for missing data will be performed).

For all continuous endpoints (primary and exploratory), the assumption of normality will be assessed. If any endpoint at any time point is found to be not normally distributed, the data will either be transformed to make it normal or a nonparametric test will be used instead of the planned ANCOVA.

The analyses described above for the primary and exploratory efficacy endpoints will be carried out using SAS (Version 9.4 or above) Proc Mixed, Proc MI, and Proc MIANALYZE as appropriate (Yuan 2000, 2011, SAS Usage Note 30715).

5.4. Statistical Analyses of Safety Measures

No statistical analyses will be performed on any of the safety data in this study. The SP will be used for all safety summarizations, with subjects included in the treatment group they actually received regardless of their randomized treatment group. AEs will be coded using definitions in the most recent version of Medical Dictionary for Regulatory Activities (MedDRA; Version 22.0.) Each AE will be coded with its appropriate Preferred Term (PT), and linked with its associated System Organ Class (SOC). AEs will be summarized using treatment-emergent AEs (TEAEs, defined as AEs that begin or worsen after the Viveve procedure [sham or active] is initiated). TEAEs and serious AEs (SAEs) will be summarized by SOC, severity, and relationship to study treatment for each treatment group. All AEs (TEAE and non-TEAE) will be provided in a listing. For screen failed subjects only AEs classified as SAEs will be reported.

No descriptive statistics are planned for vital signs or safety laboratory measurements, but data will be available in a listing.

5.5. Mid-study Analysis

A prospective analysis was to be performed after ~80 subjects have completed their 3-month visit. However, prior to this time, the sponsor decided not to perform the Mid-Study Analysis in order to maintain the LIBERATE International study integrity. The Mid-Study Analysis could potentially impact study data integrity.

When the last subject has completed her 6-month visit, the final database lock will occur for all data for all subjects. At this time, the database will be fully unblinded and all protocol-defined analyses and summaries will occur.

5.6. Sample Size Justification

The primary efficacy endpoint for this study is CFB to 6 months post-treatment in the 1-hr pad weight. A clinically meaningful reduction in the 1-hr pad weight is >50% (target reduction in the active treatment group); a sham (placebo) effect of a 30% reduction is anticipated in the sham group. The sample size for this study will be ~99 randomized subjects, in a 2:1 ratio with ~66 randomized to the active treatment group and ~33 to the sham treatment group. Assumptions include a 2-sided t-test at the 5% level of significance, and a CFB to 6 months post-treatment of >50% in the active group and of 30% in the sham group. Thus, 99 total randomized subjects, in a 2:1 ratio to active: sham treatment groups, will provide approximately 90% power if the common standard deviation in CFB is as large as 28, and will provide approximately 80% power if the common standard deviation in CFB is as large as 33. Additionally, for the CFB to 6 months post-treatment in 1-hr pad weight, a sample size of 99 total randomized subjects, in a 2:1 ratio to active:sham treatment groups, will provide approximately 90% power if the effect size (difference in treatment means divided by the standard deviation) is as small as 0.698 and approximately 80% power if the effect size is as small as 0.603. Note that an effect size of 0.698 would be achieved if the difference between active and sham groups, in CFB to 6 months post-treatment, was 25 g and the standard deviation was 35.8; and an effect size of 0.603 would be achieved if the difference was 25 g and the standard deviation was 41.4.

5.7. Experiment Design and Randomization

5.7.1. Experimental Design

This is a randomized, double-blind, sham-controlled clinical study. The study is designed to demonstrate that active treatment (the Viveve Treatment, SUI protocol) is superior to the sham treatment for the efficacy endpoint, 1-hr pad weight test, and is deemed to have appropriate safety as compared to sham. Approximately ninety-nine (99) subjects meeting the inclusion and exclusion criteria will be randomized on Study Day 1 in a 2:1 ratio to either the active or sham treatment group. Randomization will be stratified by study site, with a maximum of 30 subjects randomized at an individual site. The active treatment group will receive a treatment dose of 90 J/cm^2 and the sham group will receive a sub-therapeutic dose of ≤1 J/cm^2.

Subjects will be followed out to a 6-month post-treatment visit.

5.7.2. Randomization

Subjects will be randomized in a 2:1 (Active:Sham) ratio. Randomization will be stratified by study site, with a maximum of 30 subjects randomized at an individual site. A randomization scheme will be employed with randomly permuted blocks. Randomization assignments will be generated by statistical software. The randomization number for each subject who is randomized will be assigned after confirmation of trial eligibility.

5.8. Handling of Dropouts and Missing Data

Subjects who discontinue the study prior to completion will not be replaced. Imputation will be utilized for the primary endpoint analysis, the description of which is found in Section 5.2. No other imputation is planned. Missing data will be considered missing at random.

5.9. Multiple Comparisons/Multiplicity

In this study, the Type 1 error is controlled at 0.05 two-sided for the primary efficacy endpoint.

The exploratory efficacy endpoints will be compared to a significance level of 0.05 two-sided. No adjustment will be made for multiplicity for these endpoints. Given the number of comparisons, all p-values for exploratory efficacy endpoints will be considered descriptive.

5.10. Checks of Validity and Robustness

Confirmatory analyses for the primary and exploratory endpoints are detailed in Section 5.2 and Section 5.3.

5.11. Subject Characteristics and Disposition

The following subject demographic characteristics will be summarized by treatment group for the FAS:

- Age
- Body Mass Index (BMI)
- Race
- Ethnic origin
- Baseline 1-hr pad weight
- Baseline 24-hr pad weight
- Baseline UDI-6, ICIQ-UI-SF, I-QOL and FSFI scores

Descriptive statistics for age, BMI, 1-hr pad weight, 24-hr pad weight, and questionnaire scores will include N, mean, standard deviation, low value, median, and high value.

Descriptive statistics for race and ethnic origin will be number (n) and percent (%).

A separate summary of Age, Race, and Ethnic origin will be provided for subjects who were classified as screen failures.

Subject disposition will be determined prior to unblinding. Disposition will include whether the subject completed the study and whether there were any protocol variances. This disposition will include the placement of each subject into the different populations, such as those who complete the study, those who withdraw from the study, the FAS, the SP, etc. A separate listing will include the reason for screen failure for subjects who were classified as screen failures.

Investigational product administration will be summarized in the SP by treatment group using summary statistics. The number of treatment pulses used, as well as the reasons for deviation from the treatment schedule will be listed.

5.12. Identification of Subgroup and Session Factors

No analyses of this type are planned.

5.13. Data Tables and Listings

5.13.1. Templates of Tables

Table templates and listing templates are found in the separate Table Shells Plan.

5.14. Derived Variables and Derived Files

5.14.1. Questionnaire Scoring

The scoring of the questionnaires (UDI-6, ICIQ-UI-SF, I-QOL and FSFI) is addressed in a separate questionnaire scoring document.

5.14.2. Coding

Medical history and adverse events will be coded using MedDRA version 22.0. Concomitant medications will be coded using WHO DDE format B3 from the March 2019 release.

5.15. Descriptive Summaries

Basic descriptive statistics of CFB to month 6 in 1-hr and 24-hr pad weight will be computed by treatment stratified by mild and moderate SUI status (O'Sullivan 2004, Krhut 2014), where SUI status is based on the baseline 1-hr or 24-hr pad weight. The FAS population will be used with observed case data.

Severity of SUI	**Mild**		**Moderate**	
Pad Weight Test	**1-hr**	**24-hr**	**1-hr**	**24-hr**
Cut offs	<11 ml	<21 ml	11 – 50 ml	21 – 74 ml

Beyond the variables discussed above, no additional data summaries are planned.

6. REFERENCES

Clinical Study Protocol: Evaluation of the Safety and Efficacy of the Viveve Treatment for Stress Urinary Incontinence. 23Oct2018.

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